REMARKS

Claims 1 - 161 were pending in the application. Claims 1 – 3, 7, 8, 10, 11, 13, 14, 16-20, 40, 57, 62, 67, 69, 75, 88, 89, 93, 114, 122, 123, 125, 127, 129 – 134, 144-147, 152-157, 159 and 160 have been amended. Claims 6 and 35 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 4-6, have been cancelled. New claims 162-189 are herein added. No new matter has been added by virtue of the amendments and claims, support being found throughout the specification and claims as originally filed.

In particular, support for the amended claims can be found in original claim 4 and page 20, line 23 throughout page 21, line 9; and page 24, line 20-24 of the application as filed. In particular, support for the new claims can be found in original claims 1, 3, 4, 8 and 10-19 and page 20, line 23 to page 21, line 9; page 24, line 20 to page 25, line 18; page 26, lines 8-17; page 27, lines 3-22; page 32, lines 23-33; page 34, line 17 to page 34, line 15; and page 51, lines 13-26.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Information Disclosure Statements

The Examiner indicates that the IDS statements filed on 3/12/04, 10/15/04 and 2/14/05 have been considered.

Claim Objections

The Examiner has objected to claim 145 "because the phrase on the fourth line "a computer program product for according to any of claims 1 – 3." (Office Action, p.2).

Applicants have corrected the grammatical error and respectfully request that the objection be withdrawn.

The Examiner has objected to claims 40, 57, 69, 75, 93, 123, 133, and 152 for omission of a period. Applicants have corrected the punctuation error and respectfully request that the objection be withdrawn.

Rejection of Claims Under 35 U.S.C. 102(b)

The Examiner has rejected claims 1, 8, 15 – 18, 24 – 25, 27, 38 – 39, 43 – 51, 54 – 57, 60, 61, 67 – 73, 78 – 8085, 87 – 93, 100 – 102, 105, 107 – 117, 120, 121, 124, 126, 131, 134 and 161 under 35 U.S.C. 102(b) as being anticipated by Klein et al. (US Patent 5,413,686; the '686 reference herein). Applicants respectfully traverse the rejection.

Claim 1, as amended, recites a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling one or more functions of a microfluidic substrate in response to received data regarding one or more substrate properties, **wherein the one or more functions comprises sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.**

Claim 2, as amended, recites a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling one or more functions of a microfluidic substrate in response to received data regarding one or more properties of a sensor in fluid communication with at least one microchannel of the substrate and

optionally, for controlling one or more functions of the microfluidic substrate in response to received data regarding one or more substrate properties and, **wherein the one or more functions comprises sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid streams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.**

Claim 3, as amended, recites a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling one or more functions of a microfluidic substrate, including **instructions for controlling the exposure of a cell based biosensor to multiple fluid streams from a plurality of outlets of the one or more microchannels in the substrate by varying the pressure of one or more of the microchannels.**

Further, new claim 162 recites a computer program product having a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling a fluid delivery control mechanisms, so that the fluid delivery control mechanism; **delivers a cell based biosensor via a fluid through a first microchannel in a micofluidic substrate to a sensor chamber comprising one or more electrodes in communication with the sensor chamber which form a patch clamp system, applies a negative pressure to a second microchannel so as to position said cell based biosensor in electrical communication with the one or more electrodes, and sequentially exposes the cell based biosensor to a plurality of fluid streams from one or more microchannels.**

To anticipate a claim, each and every element of the claim must be found in a single reference. This is discussed in the Manual of Patent Examining Procedure § 2131:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The '686 reference does not teach or suggest all the limitations of the instant claims. In particular, the '686 reference nowhere teaches or suggests any cell based biosensor or instructions for sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels (claims 1 and 2, and dependent claims thereof) or instructions for controlling the exposure of a cell based biosensor to multiple fluid streams from a plurality of outlets of the one or more microchannels in the substrate by varying the pressure of one or more of the microchannels. (claim 3 and dependent claims thereof)

Nowhere does the '686 reference, expressly or inherently, teach or describe a cell based sensor, or any use for a cell based sensor in the methods or systems as claimed. The '686 reference is directed to an automated ***capillary electrophoresis*** analyzer that can simultaneously analyze a number of samples.

In some embodiments the invention is directed to computer program products and systems for performing high throughput screening (HTS) assays using microfluidic substrates. In particular, the invention provides computer program products for integrating functions and movements in a microfluidic substrate such as cell movements and data acquisition. In further embodiments, the invention is directed to an automated system which is useful for identifying compounds which interact with cells (e.g., ligands which bind cellular receptors). The present claims recite computer program products,

workstations, systems and methods of use thereof, for use with microfluidic substrates so as to expose a cell based biosensor to multiple fluid streams. In some embodiments, the product further requires detecting an electrical property of the cell based biosensor, e.g., upon stimulation with a ligand which binds to a receptor of the cell based biosensor.

The '686 reference is directed to a **capillary electrophoresis (CE)**. The presently claimed invention is not directed to "capillary electrophoresis" and nowhere in the claims is this term recited. However, even though the claims are not directed to capillary electrophoresis that is not to say the claimed device could not further include a CE component.

Similarly, with respect to the new claims, the '686 references, does not expressly or inherently teach or describe a computer product or system with instructions for delivering a cell based biosensor via a fluid through a first microchannel in a micofluidic substrate to a sensor chamber comprising one or more electrodes in communication with the sensor chamber which form a patch clamp system, apply a negative pressure to a second microchannel so as to position said cell based biosensor in electrical communication with the one or more electrodes, and sequentially exposes the cell based biosensor to a plurality of fluid streams from one or more microchannels. Based on the foregoing, Applicants submit that the claims are not anticipated by the '686 reference.

Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Rejection of Claims Under 35 U.S.C. 103(a)

The Examiner has rejected claims 2 – 6, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97, 98, 100 – 122, 124, 126 – 134, 137 – 139, 142 – 149, 151, 153 – 155 and 159 – 161 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) as applied to claims 1, 8, 15 – 18, 24, 25, 27, 38, 39, 43 – 51, 54 – 57, 60, 61, 67 – 73, 78 – 80, 85, 87 – 93, 100 – 102, 105, 107 – 117, 120, 121, 124, 126, 131,

134 and 161 as above, and further in view of Agilent (Agilent capillary electrophoresis system, brochure). (Office Action, p.7).

The Examiner has rejected claims 14, 19 – 23, 99 and 156 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 2 – 6, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97, 98, 100 – 122, 124, 126 – 134, 137 – 139, 142 – 149, 151, 153 – 155 and 159 – 161 above, and further in view of Colton et al. (Electrophoresis, 1998, vol. 19, pages 367 – 382). (Office Action, p.16).

The Examiner has rejected claims 34, 40 – 42, 150 and 152 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 2 – 6, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97, 98, 100 – 122, 124, 126 – 134, 137 – 139, 142 – 149, 151, 153 – 155 and 159 – 161 above, and further in view of Katayama et al. (Analytical Chemistry, 1998, vol. 70, pages 2254 - 2260). (Office Action, p.17).

The Examiner has rejected claims 95 – 96, 123, 135, 136, 140, 141, 157 and 158 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 2 – 6, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97, 98, 100 – 122, 124, 126 – 134, 137 – 139, 142 – 149, 151, 153 – 155 and 159 – 161 above, and further in view of Jardemark et al. (Analytical Chemistry, 1997, vol. 69, pages 3427 - 3434). (Office Action, p.19).

The Examiner has rejected claim 125 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 2 – 6, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97, 98, 100 – 122, 124, 126 – 134, 137 – 139, 142 – 149, 151, 153 – 155 and 159 – 161 above, and further in view of Couderc et al. (Electrophoresis, 1998, vol. 19, pages 2777 - 2790). (Office Action, p.21).

For the sake of brevity, the rejections under 103(a) are addressed together because each rejection relies on the '686 reference in view of the Agilent brochure in combination with another reference.

Applicants respectfully traverse the forgoing rejections.

As described above in detail, Applicant's claims describe a computer program product with instructions for sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels (claims 1 and 2); and (claim 3) instructions for controlling the exposure of a cell based biosensor to multiple fluid streams from a plurality of outlets of the one or more microchannels in the substrate by varying the pressure of one or more of the microchannels.

Further, new claim 164 recites a computer program product having instructions for controlling a fluid delivery control mechanisms, so that the fluid delivery control mechanism; delivers a cell based biosensor via a fluid through a first microchannel in a micofluidic substrate to a sensor chamber comprising one or more electrodes in communication with the sensor chamber which form a patch clamp system, applies a negative pressure to a second microchannel so as to position said cell based biosensor in electrical communication with the one or more electrodes, and sequentially exposes the cell based biosensor to a plurality of fluid streams from one or more microchannels.

Applicants submit that the combination of references does not teach or suggest the invention as claimed. Nowhere does the '686 reference teach or suggest any cell based biosensor or computer product, workstation, system or method for sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels (claims 1 and 2, and dependent claims thereof) or instructions for controlling the exposure of a cell based biosensor to

multiple fluid streams from a plurality of outlets of the one or more microchannels in the substrate by varying the pressure of one or more of the microchannels. (claim 3 and dependent claims thereof).

Further, none of Agilent, Colton, Katayama, Jaredemark or Couderc alone or in combination with Klein et al. teach or suggest all the elements or the claims, and none of the references provide any motivation to use a cell based biosensor with the expectation of sequentially exposing the cell based biosensor in an automated fashion to multiple fluid streams.

The MPEP at 2100-119 provides the following explanation of what constitutes a proper rejection under 35 U.S.C. 103:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S., 82 USPQ2d at 1396.

According to the MPEP, among the exemplary rationales that may support a conclusion of obviousness are included:

> (A)Combining prior art elements according to known methods to yield predictable results;
> (B)Simple substitution of one known element for another to obtain predictable results;
> (C)Use of known technique to improve similar devices (methods, or products) in the same way;
> (D)Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
> (E)"Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
> (F)Known work in one field of endeavor may prompt variations of it for use in either the same field or a different

> one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
> (G)Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention

Further, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*KSR v. Teleflex*, 550 U.S. ___, 127 S. Ct. 1727 (2007)). Second, there must be a reasonable expectation of success. *Id.* The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *Id.* The prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Furthermore, the Court of Customs and Patent Appeals has held that "[r]eferences relied upon to support a rejection under 35 U.S.C. 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." (*In re Payne, Durden, and Weiden*, 203 U.S.P.Q. 245, 255 (C.C.P.A. 1979)). "In the absence of proper *prima facie* case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent." *In re Rouffet*, 149 F. 3d 1350 (Fed. Cir. 1998).

The Examiner has failed to support the instant rejections under 35 U.S.C. 103(a) with any reasons of why the claimed invention would have been obvious according to the standards outlined in the MPEP.

The '686 reference "is directed to a **capillary electrophoresis (CE)** analyzer that can simultaneously analyze a plurality of samples." (col 3, line1). The '686 reference does not teach or suggest the invention as claimed. In fact, nowhere is "capillary electrophoresis" recited in the present claims. The presently claimed device is not directed to a capillary electrophoretic device, although the claimed device may be envisioned to further include a capillary electrophoretic component. As shown in Figures

4 and 5, below, the CE system of the '686 reference includes wells that receive capillary ends (see, e.g. claim 1) wherein the well contains reagent sample. Figures 4 and 5 are shown below.

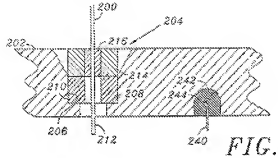

FIG. 4

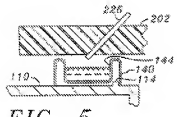

FIG. 5

Referring to Figures 4 and 5, beginning at col. 6, line 18:

> the sample ends of the capillaries 200 are removably supported by a sample end plate 202. The sample end plate 202 is generally arcuate and includes six capillary end retainers 204 (FIG. 4). The vertical center lines of the capillary end retainers 204 are spaced to align with the spacing between corresponding ones of the reservoirs 144 within the reservoir groups 142 of a reagent segment 140 positioned on the turntable 100. This spacing aligns the ends of the capillaries 200 over, for example, a first one of the reservoirs 144 within each reservoir group 142 when so positioned by the rotation of the turntable, and so on.
>
> To be retained by the sample end plate 202, sample end 212 of each of the capillaries 200 includes a second polarized barium ferrite annular magnet 214 bonded to the capillary 200 proximate the sample end 202 by means of a suitable rubber adhesive 216. With the capillary 200 positioned as illustrated in FIG. 4, the abutting ends of the magnets 210

> and 214 are reverse polarized respectively, creating an attractive magnetic force between the magnets 214 and 210. The magnetic force thereby removably retains the capillary 200 within the sample end plate 202 and positions the sample end 212 for access to reservoirs 144 within a reagent segment 140 that may be carried by the turntable 100.

Further, nowhere does the '686 reference teach a cell based biosensor or sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

The instant disclosure teaches computer program products and systems for performing screening assays (preferably high throughput) using microfluidic substrates. In particular, the claims are directed to a computer program product, workstations, methods and systems thereof, where the program product comprises instructions for sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

All claims require a "cell based biosensor". The specification describes a cell based biosensor as:

> As used herein, the term, "a cell-based biosensor" refers to an intact cell or a part of an intact cell (e.g., such as a membrane patch) which is capable of providing a detectable physiological response upon sensing a condition in an aqueous environment in which the cell (or part thereof) is placed. In one aspect, a cell-based biosensor is a whole cell or part of a cell membrane in electrical communication with an electrically conductive element, such as a patch clamp electrode or an electrolyte solution.

Figures 12 illustrates embodiments of the claimed computer program products and systems for performing high throughput screening (HTS) assays using microfluidic substrates. Figure 12 is shown below:

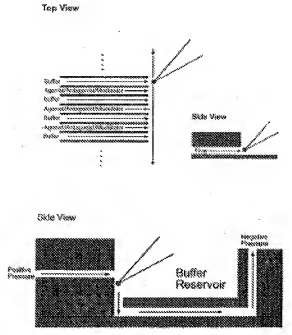

FIGURE 12A-C

Figure 12A schematically depicts an embodiment in which the top view of a microfluidic substrate comprises interdigitating channels and in which a patch-clamped cell is being moved past the outlets of the channels. FIGS. 12B and 12C depict side views of alternate embodiments of the outlets and microchannels. FIGS. 12B and 12C are side views showing a 2D and 3D microfluidic chip design, respectively.

Further, the specification teaches that the cell based biosensor may be stationary and exposed to a plurality of fluid steams:

> As used herein, "scanning of a sensor relative to one or more channels in a microfluidic substrate" refers to exposure of the sensor to a plurality of fluid streams from at least one channel in the substrate. . . Exposure to a plurality of fluid streams from a single channel may be achieved by providing different fluid streams (e.g., comprising different agents, or

different doses of the same agent, or alternating buffer flow and flow of fluid stream containing an agent, or some combination thereof) from the single channel and/or by intermittently stopping the flow of fluid from an outlet of the channel in proximity to the sensor. In an embodiment where the sensor is stationary, scanning can be done by varying pressure at one or more channels.

[Page 20, line 23 to page 21, line 7]

Neither the '686 reference, nor any of the other cited documents disclose or suggest sequentially exposing a cell based biosensor to multiple fluid steams from one or more microchannels in a substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels as Applicants disclose and claim.

The Examiner argues that the Agilent reference "is a brochure describing the benefits of using an Agilent capillary electrophoresis system for measuring biolmolecules (and) the fourth page of the brochure measures the migration time of an oligonucleotide sensor." (Office Action, p.8). The Examiner argues that "(t)he brochure itself gives instructions for detecting sensors using the CE apparatus in the form of specification on the penultimate page of the brochure." (Office Action, p.8). Referring to Figure 4 of the Agilent brochure, the Examiner argues that "(i)t would have been obvious to someone of ordinary skill in the art...to modify the capillary electrophoresis apparatus of (the '686 reference) by use of the sensors, agents and capillary electrophoresis apparatus of the Agilent brochure wherein the motivation would have been that the use of a sensor gives the apparatus an entity which to measure migration time (i.e. the Figure on the fourth page of Agilent)." (Office Action, p.15). The Examiner argues further that "the multiple capillaries in the apparatus with the computer system (of the '686 reference) enable multiple experiments to be performed at once." (Office Action, p.15).

Agilent fails to remedy the deficiencies of the '686 reference. Agilent merely teaches a **CE system** that for the analysis of oligonucleotides and other small molecules. CE is used to separate ionic species by their charge and frictional forces. In contrast, embodiments of the presently claimed invention are directed to program products, systems, workstations and methods which transport cell based biosensors and the agents which interact with the cell based biosensor via a pressure driven fluid

flow. Nowhere does the Agilent brochure disclose or suggest the claimed invention in which a cell based biosensor is sequentially exposed to multiple fluid steams from one or more microchannels in a substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

None of Colton, Katayama, Jarademark or Couderc remedies the flaws of the '686 and the Agilent references. None of Colton, Katayama, Jarademark or Couderc teaches or suggests.

In particular, the Action states that:

> Jadermark et al. illustrates the patch clamp procedure with the cellular components undergoing electrophoresis (i.e., the sensor comprises fragments of the cell). The caption of Figure 1 indicates that the setup is capable of being manipulated with "micromanipulators." It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and Agilent by use of the patch clamp capillary electrophoresis apparatus of Jardemark et al. . . .

Applicants disagree.

Applicants assert that the pending claims are non-obvious in light of Jardemark et al., Klein et al. and Agilent because the prior art fails to provide motivation to combine the prior art teachings to arrive at the claimed invention, fails to teach each and every element of the pending claims, fails to provide a reasonable expectation of success.

As described above, Klein et al. and Agilent fail to teach or suggest sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid steams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

Further, in the embodiments of the new claims the present invention utilizes a program product to automate a microfluidic chip which is operative coupled to a fluid delivery system so as to sequentially expose a cell based biosensor to multiple fluid streams. The microfluidic chip delivers a cell based biosensor via a fluid through a first microchannel in a micofluidic substrate to a sensor chamber having a patch clamp; a negative pressure is applied in a second microchannel so as to position the cell based

biosensor so that it is in electrical communication with the one or more electrodes of the patch clamp. The patch clamped cell is then sequentially exposes to a plurality of fluid streams from one or more microchannels. Generally, these fluid streams will each contain different potential ligands which interact with the cell based biosensor. This is not taught or suggested by any of the cited art.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Dated: December 2, 2008

Respectfully submitted,

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